PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference NEREUS.079VP	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2004/019543	International filing date (*day/month/year*) 18 June 2004 (18.06.2004)	Priority date (*day/month/year*) 20 June 2003 (20.06.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant NEREUS PHARMACEUTICALS, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 20 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 03 January 2006 (03.01.2006)
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PATENT COOPERATION TREATY

REC'D 02 MAR 2005
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From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/019543	18.06.2004	20.06.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/407, A61P35/00, A61P35/02, A61P29/00, A61P19/02, A61P11/06, A61P25/00, A61P17/06, A61P9/10,

Applicant
NEREUS PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/019543

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/019543

Box No. II Priority

1. ☐ The following document has not been furnished:

   ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☒ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/019543

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-24 (all partially)

because:

☒ the said international application, or the said claims Nos. 1-14 and 17-24 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-24 (all partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/019543

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	6-8, 13, 16, 21-24
	No: Claims	1-5, 9-12, 14, 15, 17-20
Inventive step (IS)	Yes: Claims	-
	No: Claims	1-24
Industrial applicability (IA)	Yes: Claims	15-16
	No: Claims	

2. Citations and explanations

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.i. Claims 1-14 and 17-24 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

III.ii. This application does not meet the requirements of Article 5 and 6 PCT, because claims 1-11 and 14-24 are not clear, nor sufficiently supported and the invention is not sufficiently disclosed by the description.

(a) Present claims 1-11 and 14-24 relate to a very large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formulae I-V wherein E1 and E3 are both O, which is a generalisation of formulae I-1 - I-6 (p. 10-15), II-1 - II-25 (p. 17-34) and IV-1 - IV-4 (p. 37-41).

(b) Moreover, present claims 1-11 and 14-20 relate to compounds which actually are not well-defined. The use of the definition "pro-drug esters thereof" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the compounds as specified under item **III.ii(a)**

(c) Present claims 19, 20 relate to the treatment of a disease which actually is not well-defined. The use of the definitions "inhibiting proteasome activity" and "inhibiting NF-kappaB activation" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is not fully possible to determine the diseases for which protection might legitimately be sought. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the real and defined diseases mentioned in claims 1-8, 14 and 17, namely cancer, with due regard to the general idea underlying the application.

(d) Present claims 21 and 23 refer to the treatment of diseases which actually are not

well defined. The use of the definitions "an inflammatory condition" and "a microbial illness" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is not fully possible to determine the diseases for which protection might legitimately be sought. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the real and defined diseases mentioned in claims 22 and 24, with due regard to the general idea underlying the application.

(e) Claims 2-11, 14-15 and 17-24 contain references to the description, namely "a compound of a formula selected from Formulae I-V". According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.

No opinion of the International Search Authority will be given in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT) (see also items **IV** and **V.i**).

Re Item IV

Lack of unity of invention

The present application lacks unity within the meaning of Rule 13.1 PCT for the following reasons:

The problem to be solved by the present application is the provision of alternative medicines for inhibiting proteasome activity and/or NF-kappaB activation, and for the treatment of diseases which can be remedied by inhibition of proteasome activity and/or NF-kappaB activation, namely cancer, inflammation or infectious diseases (see e.g. description, p. 49, par. [206]-[208]).

The proposed solution is the use of compounds of formulae I-V.

Thus, in the context of the alleged invention, the use of compounds of formulae I-V for inhibiting proteasome activity and/or NF-kappaB activation, and for the treatment of diseases which can be remedied by inhibition of proteasome activity and/or NF-kappaB activation, namely cancer, inflammation or infectious diseases, is the alleged contribution over the prior art and the special technical feature which may, a priori, unify the plurality of different inventions.

The use of compounds of formulae I-V for inhibiting proteasome activity and/or NF-kappaB activation has been previously disclosed.

See e.g. XP002304842 (D1) and XP008038137 (D2), which disclose that salinosporamide A is a potent 20S proteasome inhibitor (XP002304842: p. 356, column 2, par. 3; XP008038137: p. 493, left-hand column, par. 1).

In addition, the use of compounds of formulae I-V for the treatment of cancer is also not novel and not inventive in the light of the prior art, which directly and unambiguously reflect this therapeutic application:

XP002304842 (D1) reports that salinosporamide A displays potent in vitro cytotoxicity against e.g. human colon carcinoma, non-small cell lung cancer, CNS cancer, melanoma and breast cancer (p. 356, column 2, par. 3).

XP008038137 (D2) teaches that salinosporamide A is in pre-clinical development for the treatment of cancer (p. 493, left-hand column, par. 1).

In WO0247610 (D3), it is disclosed that salinosporamide A is a highly potent anti-cancer agent, which shows in vitro anti-cancer activity against the HCT-116 human colon carcinoma (p. 9, par. 2 - p. 10, par. 1).

XP002304843 (D4) states that salinosporamide is particularly efficient against colon carcinoma, lung and breast cancer.

The idea to use compounds of formulae I-V for inhibiting proteasome activity and/or NF-kappaB activation, and for the treatment of diseases which can be remedied by inhibition of proteasome activity and/or NF-kappaB activation, namely cancer, inflammation or infectious diseases, is not novel; it can therefore not fulfil the role of special technical feature in the sense of Rule 13.1 PCT.

In the present application no further technical feature can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions. Consequently the present application lacks unity of invention. Each of the inventions listed is a distinct invention, characterised by its own special technical feature, defining the contribution which each of the claimed inventions, considered as a whole, makes over the prior art, i.e. the specific features of the individual diseases.

It is to be noted that claim 16 has been included in the third invention, based on paragraph [0229] on p. 56 of the present description.

Hence the International Authority considers that the following separate inventions or groups of inventions are not so linked as to form a single general inventive concept:

1. Claims: 1 (partially), 2-15 (entirely), 17-20 (entirely)

Use of a compound having the structure of formula I, and pharmaceutically acceptable salts and pro-drug esters thereof in the treatment of cancer.

A method of treating a neoplastic disease in an animal, the method comprising administering to the animal a therapeutically effective amount of a compound of a formula selected from formulae I-V, and pharmaceutically acceptable salts and pro-drug esters thereof.

A pharmaceutical composition comprising a compound of a formula selected from formulae I-V, and pharmaceutically acceptable salts and pro-drug esters thereof, without an anti-microbial agent.

A method of inhibiting the growth of a cancer cell comprising contacting a cancer cell with a compound of a formula selected from formulae I-V, and pharmaceutically acceptable salts and pro-drug esters thereof.

A method of inhibiting proteasome activity or of inhibiting NF-kappaB activation comprising the step contacting a cell with a compound of a formula selected from formulae I-V, and pharmaceutically acceptable salts and pro-drug esters thereof.

2. Claims: 1 (partially), 21-22 (entirely)

Use of a compound having the structure of formula I, and pharmaceutically acceptable salts and pro-drug esters thereof in the treatment of inflammation.

A method for treating an inflammatory condition comprising administering an effective amount of a compound of a formula selected from formulae I-V to a patient in need thereof.

3. Claims: 1 (partially), 16 (entirely), 23-24 (entirely)

Use of a compound having the structure of formula I, and pharmaceutically acceptable salts and pro-drug esters thereof in the treatment of infectious disease.

A pharmaceutical composition comprising a compound of a formula selected from formulae I-V, and pharmaceutically acceptable salts and pro-drug esters thereof and an anti-microbial agent.

A method for treating a microbial illness comprising administering an effective amount of a compound of a formula selected from formulae I-V to a patient in need thereof.

As the Applicant has had a search report drawn up for all inventions, **the application will be prosecuted on the basis of the inventions in respect of which a search has been carried out, in other words the entire application, i.e. claims 1-24.**

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.i. (a) Attention is drawn to the fact that the present statement expressed as to novelty, inventive step and industrial applicability refers only to matter for which an International Search Report has been drawn up (i.e. only for the use of compounds of formulae I-V wherein E1 and E3 are both O, for the treatment of cancer, an inflammatory condition as defined in claim 22 or a microbial illness as defined in claim 24, and for pharmaceutical compositions containing such compounds, with due regard to the general idea underlying the application).

(b) Present claims 1-14 and 17-24 involve compositions or substances in a method of treatment of the human/animal body. For the assessment of such claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

V.ii. The following documents are referred to in this communication:

D1 : FELING ROBERT H ET AL: "Salinosporamide A: a highly cytotoxic proteasome inhibitor from a novel microbial source, a marine bacterium of the new genus salinospora." ANGEWANDTE CHEMIE (INTERNATIONAL ED. IN ENGLISH), (2003 JAN 20) 42 (3) 355-7. JOURNAL CODE: 0370543. ISSN: 0570-0833., 20 January 2003 (2003-01-20), XP002304842

D2 : FENICAL W. ET AL: "Marine microorganisms as a developing resource for drug

discovery." PHARMACEUTICAL NEWS, 9/6 (489-494). REFS: 14 ISSN: 1071-894X CODEN: PHNEEP, 2002, XP008038137

D3 : WO 02/47610 A (UNIV CALIFORNIA) 20 June 2002 (2002-06-20)

D4 : [Online] XP002304843 Retrieved from the Internet: URL:http://www.newton.rcs.it/PrimoPiano/News/2003/02_Febbraio/03/Antobiotico.shtml>; [retrieved on 2003-02-02]

D5: GOLDBERG, ALFRED L. ET AL: "Not just research tools- proteasome inhibitors offer therapeutic promise" NATURE MEDICINE (NEW YORK, NY, UNITED STATES) , 8(4), 338-340 CODEN: NAMEFI; ISSN: 1078-8956, 2002, XP008038140

D6: NICOLAUS B J R: "Symbiotic Approach to Drug Design" DECISION MAKING IN DRUG RESEARCH, XX, XX, 1983, pages 173-186, XP002197412

D7: WO 96/32105 A (PRESIDENT AND FELLOWS OF HARVARD COLLEGE; SCHREIBER, STUART, L; STANDA) 17 October 1996 (1996-10-17)

D8: WO 00/23614 A (LEUKOSITE, INC; MILLENNIUM PHARMACEUTICALS, INC) 27 April 2000 (2000-04-27)

D9: ELLIOTT, PETER J. ET AL: "The proteasome : A new target for novel drug therapies" AMERICAN JOURNAL OF CLINICAL PATHOLOGY , 116(5), 637-646 CODEN: AJCPAI; ISSN: 0002-9173, 2001, XP008007324

D10: CRANE, SHELDON N. ET AL: "A Novel Enantioselective Synthetic Route to Omuralide Analogues with the Potential for Species Selectivity in Proteasome Inhibition" ORGANIC LETTERS , 3(9), 1395-1397 CODEN: ORLEF7; ISSN: 1523-7060, 2001, XP008038134

D11: GANTT, SOREN M. ET AL: "Proteasome inhibitors block development of Plasmodium spp." ANTIMICROBIAL AGENTS AND CHEMOTHERAPY , 42(10), 2731-2738 CODEN: AMACCQ; ISSN: 0066-4804, 1998, XP008038135

D12: TANG GUANGQING ET AL: "Proteasome activity is required for anthrax lethal toxin to kill macrophages" INFECTION AND IMMUNITY, vol. 67, no. 6, June 1999 (1999-06), pages 3055-3060, XP008038136 ISSN: 0019-9567

D13: BEERS M., BERKOW R.: "The Merck Manual of Diagnosis and Therapy, seventeenth edition" 1999, MERCK RESEARCH LABORATORIES , WHITEHOUSE STATION N.J. , XP002318189

D14: WO 2005/003137 A (THE REGENTS OF THE UNIVERSITY OF

CALIFORNIA; FENICAL, WILLIAM, H; JENS) 13 January 2005 (2005-01-13)

V.iii. Article 33(2) PCT.

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-5, 9-12, 14, 15 and 17-20 is not new in the sense of Article 33(2) PCT.

(a) The documents cited below (D1-D4) all demonstrate the *in vitro* anti-cancer activity of the presently claimed compounds.

It is a well-established and accepted principle that, for the purpose of patent protection of a medical application of a substance, a pharmacological effect or any other effect such as a behavioural effect observed either *in vitro* or on animal models is accepted as sufficient evidence of a therapeutic application if for the skilled person this observed effect directly and unambiguously reflects such a therapeutic application.

In addition, in spite of the numerous examples in the description, none goes further than *in vitro* anti-cancer experiments (examples 18, 19, 32-35 and 40-42). Therefore, the description provides no further evidence or data showing the actual anti-cancer effect of the compounds of formulae I-V in humans or animals than did the prior art documents D1-D4.

Accordingly, in the absence, in the patent application as originally filed, of any data providing additional technical information in relation to the actual treatment of cancer in humans or animals compared with the disclosure in the prior art documents D1-D4 (see below), it must be concluded that the subject-matter of the patent application is anticipated by the disclosures in D1-D4, i.e. those documents disclose the same "therapeutic application" as the present application.

(b) Claims 19 and 20 relate to the mechanisms underlying the treatment of the claimed diseases with the compounds of the present invention. However, the mere explanation of an effect obtained when using a compound in a known composition, even if the effect was not known to be due to this compound in the known composition, cannot confer novelty on a known process if the skilled person was already aware of the occurrence of the desired effect. Even if the inhibition of proteasome activity and of NF-kappaB activation by the compounds of the present invention is indisputably a pharmacological effect, it cannot in itself be considered a therapeutic application, nor can it render the known treatment of a specified

pathological condition, in the present case the known treatment of cancer, novel. Although the discovery of such a mechanism may be an important piece of scientific knowledge, it cannot be considered as a technical contribution to the art, since it still needs to be turned into a practical application in the form of a specified actual treatment of the pathological condition. In the present case, the specified actual treatment of the pathological condition cancer was already disclosed in the cited prior art documents D1-D4 (see below).
Consequently, whatever the merit of the scientific teaching provided by the application regarding the mechanism of action of the claimed compounds, it is only the therapeutic effect of the medicament, i.e. treating cancer, which is relevant for the assessment of novelty and inventive step.

(c) Document D1 reports that salinosporamide A, which is a potent inhibitor of 20S proteasome, displays potent *in vitro* cytotoxicity against e.g. human colon carcinoma, non-small cell lung cancer, CNS cancer, melanoma and breast cancer (p. 356, column 2, par. 3). Therefore, and in view of items **V.iii(a)-(b)**, the subject-matter of present claims 1-5, 9-12, 14, 15 and 17-20 is not novel over D1.

(d) Document D2 teaches that salinosporamide A is in pre-clinical development at Nereus. It is a proteasome inhibitor, targeted toward the treatment of cancer (p. 493, left-hand column, par. 1). Therefore, and in view of items **V.iii(a)-(b)**, the subject-matter of present claims 1-3, 9-12, 14, 15, 17 and 19-20 is not novel over D2.

(e) In document D3, it is disclosed that salinosporamide A is a highly potent anti-cancer agent, which shows *in vitro* anti-cancer activity against the HCT-116 human colon carcinoma (p. 9, par. 2 - p. 10, par. 1). Therefore, and in view of items **V.iii(a)-(b)**, the subject-matter of present claims 1-4, 9-12, 14, 15, 17 and 19-20 is not novel over D3.

(f) Document D4 states that salinosporamide is particularly efficient against colon carcinoma, lung and breast cancer. Therefore, and in view of items **V.iii(a)-(b)**, the subject-matter of present claims 1-4, 9-12, 14, 15, 17 and 19-20 is not novel over D4.

V.iv. Article 33(3) PCT.

(a) The first problem to be solved by the present application is the provision of alternative medicines for the treatment of cancer.

(b) The second problem to be solved by the present application is the provision of alternative medicines for the treatment of an inflammatory condition.

(c) The third problem to be solved by the present application is the provision of alternative medicines for the treatment of a microbial illness.

(d) Claims 1-11 and 14-24 of the present application relate to a very wide variety of compounds which all are supposed to be effective in the treatment of cancer, an inflammatory condition or a microbial illness (see also item **III.ii(a)**).

By virtue of the many possible substituents, which in themselves at least in part will represent further pharmacophoric moieties, it appears to be highly questionable that it is predictable that all claimed variants actually will exhibit the claimed properties in relation to the treatment of cancer, an inflammatory condition or a microbial illness. The skilled person is aware of the fact that the effects of such hybrid compounds comprising more than one pharmacophoric group cannot be foreseen having regard to the preparation of a medicament for the claimed therapeutic utility (see also D6). The presence of an inventive step can only be recognised for problems which have been solved by all claimed variants.

(e) As far as the treatment of cancer is concerned, the following is to be noted:

1. Even if novelty could be restored, the present application would very likely lack an inventive step over each of D1-D4, which clearly suggest the use of compounds of formulae I-V for the treatment of cancer.

2. As far as the treatment of drug-resistant cancers (claims 6-8) is concerned, the present application does not - at present - involve an inventive step for the following reasons:

Document D5 discloses that proteasome inhibitors, due to their ability to block activation of NF-kappaB, have anti-apoptotic effects and can sensitize cancer cells to other anti-cancer treatments, such as DNA-damaging agents and Taxol (p. 340, middle column, par. 3). This implies that proteasome inhibitors can be used to treat drug-resistant cancer cells.

As from D1 and D2, it is known that salinosporamide A is a highly potent proteasome inhibitor (see items **V.iii(c)-(d)**), it was obvious for the person skilled in the art to at least try to use salinosporamide A and related compounds for the treatment of drug-resistant cancers, with a reasonable expectation of success.

3. As far as the subject-matter of present claim 13 is concerned, the present application does not - at present - involve an inventive step for the following reasons:

From each of D1-D4, the anti-cancer activity of salinosporamide A is known. Since the compound of present claim 13 appears merely to be a variation of a structurally related compound without any documented unexpected technical effect, the subject-matter of claim 13 is at present regarded as obvious.

(f) As far as the treatment of an inflammatory condition is concerned, the present

application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 21 and 22 does not involve an inventive step in the sense of Article 33(3) PCT for the following reasons:

1. Each of documents D5 and D7-D9 disclose the use of proteasome inhibitors, which are structurally related to the presently claimed compounds, for the treatment of inflammatory disorders:

Document D5 discloses that proteasome inhibitors, such as PS-519, a 6-oxa-2-azabicyclo-[3.2.0]heptane-3,7-dione, can be used for the treatment of inflammation, such as psoriasis, asthma, arthritis, infarcts, strokes ... (p. 338, column 2, par. 1 - column 3, par. 1; p. 339, column 1, par. 2; passage bridging columns 2 and 3; p. 340, column 1, par. 2; column 2, par. 2).

Document D7 teaches the use of selective proteasome inhibitors, such as lactacystin β-lactone, for the treatment of diseases mediated by the proteolytic function of the proteasome or indirectly via proteins which are processed by the proteasome such as NF-κB, such as inflammation and inflammation associated with asthma or allergies, rheumatoid arthritis, psoriasis or multiple sclerosis (p. 3, line 33 - p. 6, line 15; p. 7, line 21 - p. 8, line 26; p. 13, line 26 - p. 14, line 12; p. 81, lines 1-14; p. 82, line 19 - p. 83, line 2; p. 84, lines 8-22; p. 85, lines 3-32; p. 90, line 16 - p. 91, line 14; claims 6, 10, 38, 40, 45-48, 53-55, 58). Other anti-inflammatory or anticancer agents may be coadministered (p. 91, lines 31-35).

Document D8 discloses the use of proteasome inhibitors, such as lactacystin and analogs thereof, such as clasto-lactacystin-β-lactone and derivatives (p. 11, lines 9-14), for the treatment of inflammatory diseases, such as rheumatoid arthritis, asthma, ischemia, stroke, myocardial infarction (p. 3, lines 3-4; p. 7, lines 6-24; p. 10, lines 14-23)

Document D9 discloses that proteasome inhibitors, such as PS-519, a synthetic agent similar to lactacystin β-lactone, can be used for the treatment of inflammation, such as asthma, ischemia and reperfusion injury, multiple sclerosis, rheumatoid arthritis, psoriasis, ... (abstract; Table 1; p. 638, right-hand column, par. 1; p. 639, right-hand column, par. 3; p. 641, left-hand column, par. 1; p. 641, left-hand column, par. 3 - p. 642, left-hand column, par. 4).

2. The subject-matter of present claims 1, 21 and 22 differs herefrom in that 6-oxa-2-azabicyclo-[3.2.0]heptane-3,7-diones are used wherein the 4-position is substituted by a substituent other than H.

3. The problem to be solved by the present invention may therefore be regarded as the provision of alternative 6-oxa-2-azabicyclo-[3.2.0]heptane-3,7-dione proteasome inhibitors for the treatment of the same diseases.

4. The solution proposed in claims 1, 21 and 22 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

As from D1 and D2, it is known that salinosporamide A is a highly potent proteasome inhibitor (see items **V.iii(c)-(d)**), which is much more potent than omuralide (= clasto-lactacystin-β-lactone) (see e.g. D1, p. 356, right-hand column, par. 3), it was obvious for the person skilled in the art to at least try to use salinosporamide A and related compounds for the treatment of inflammatory conditions, with a reasonable expectation of success.

5. In conclusion, in the absence of comparative data and/or convincing arguments showing a surprising effect when using Salinosporamide A and its derivatives for the treatment of inflammatory disorders over the prior art compounds lactacystin β-lactone and PS-519, an inventive step cannot be recognised at present.

(g) As far as the treatment of a microbial illness is concerned, the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 16, 23 and 24 does not involve an inventive step in the sense of Article 33(3) PCT for the following reasons:

1. Each of documents D7-D9 disclose the use of proteasome inhibitors, which are structurally related to the presently claimed compounds, for the treatment of microbial illnesses:

Document D7 teaches the use of selective proteasome inhibitors, such as lactacystin β-lactone, for the treatment of diseases mediated by the proteolytic function of the proteasome or indirectly via proteins which are processed by the proteasome such as NF-κB, such as chronic infectious diseases, such as reducing or inhibiting HIV infection (p. 3, line 33 - p. 6, line 15; p. 7, line 21 - p. 8, line 26; p. 81, lines 1-14; p. 82, line 19 - p. 83, line 2; p. 84, lines 8-22; claims 6, 10, 38, 40). Other anti-inflammatory or anticancer agents may be coadministered (p. 91, lines 31-35).

Document D8 discloses the use of proteasome inhibitors, such as lactacystin and analogs thereof, such as clasto-lactacystin-β-lactone and derivatives (p. 11, lines 9-14), for the treatment of HIV infection or protozoan parasitic diseases (p. 7, lines 6-24; p. 10, lines 14-23)

Document D9 discloses that proteasome inhibitors, such as PS-519, a synthetic agent similar to lactacystin β-lactone, can be used for the treatment of HIV and other viral infections (abstract; Table 1; p. 641, left-hand column, par. 2).

2. The subject-matter of present claims 1 and 23 differs herefrom in that 6-oxa-2-azabicyclo-[3.2.0]heptane-3,7-diones are used wherein the 4-position is substituted

by a substituent other than H.

3. The problem to be solved by the present invention may therefore be regarded as the provision of alternative 6-oxa-2-azabicyclo-[3.2.0]heptane-3,7-dione proteasome inhibitors for the treatment of the same diseases.

4. The solution proposed in claims 1 and 23 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

As from D1 and D2, it is known that salinosporamide A is a highly potent proteasome inhibitor (see items **V.iii(c)-(d)**), which is much more potent than omuralide (= clasto-lactacystin-β-lactone) (see e.g. D1, p. 356, right-hand column, par. 3), it was obvious for the person skilled in the art to at least try to use salinosporamide A and related compounds for the treatment of microbial illnesses, with a reasonable expectation of success.

5. Moreover, it appears that the problem underlying the application has not been solved over the whole of the scope of claims 1 and 23: The post-published document D14 states on p. 17, par. [0051] and in example 2 that "Salinosporamide A ... shows little antifungal activity against *C. albicans* and no antibacterial activity (*S. aureus, E. faecium*)." An invention can be regarded as patentable only if and as far as the problem underlying the application actually is solved by all claimed variants.

6. As far as the treatment of *B. anthracis, Plasmodium, Leishmania and Trypanosoma* is concerned, the subject-matter of claim 24 does not involve an inventive step in the sense of Article 33(3) PCT for the following reasons:

Document D10 reports that the proteasome inhibitors lactacystin and omuralide block the development of *Plasmodium sp.* and *Trypanozoma c.* (p. 1395, left-hand column, par. 1 - p. 1396, right-hand column, par. 1).

Document D11 discloses that lactacystin or clasto-lactacystin-β-lactone inhibit the development of *Plasmodium sp.* (abstract; p. 2731, right-hand column, par. 2; Figure 5; p. 2736, left-hand column, par. 2; passage bridging p. 2736 and p. 2737).

Document D12 teaches that the proteasome inhibitor lactacystin is a very potent blocker of the cytotoxicity of the Anthrax lethal toxin (abstract; p. 3055, right-hand column, par. 3; Figure 1; p. 3056, right-hand column, par. 2; p. 3058, left-hand column, par. 3 - right-hand column, par. 1).

The subject-matter of present claims 1 and 24 differs herefrom in that 6-oxa-2-azabicyclo-[3.2.0]heptane-3,7-diones are used wherein the 4-position is substituted by a substituent other than H.

The problem to be solved by the present invention may therefore be regarded as the

provision of alternative 6-oxa-2-azabicyclo-[3.2.0]heptane-3,7-dione proteasome inhibitors for the treatment of the same diseases.

The solution proposed in claims 1 and 24 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

As from D1 and D2, it is known that salinosporamide A is a highly potent proteasome inhibitor (see items **V.iii(c)-(d)**), which is much more potent than omuralide (= clasto-lactacystin-β-lactone) (see e.g. D1, p. 356, right-hand column, par. 3), it was obvious for the person skilled in the art to at least try to use salinosporamide A and related compounds for the treatment of the specific microbial illnesses claimed in claim 24, with a reasonable expectation of success.

7. As far as the coadministration with other anti-microbial agents is concerned (claim 16), this subject-matter does not - at present - involve an inventive step for the following reasons:

From D14, it is known that microbial illnesses, including *B. anthracis, Plasmodium, Leishmania and Trypanosoma* can be treated with anti-microbial agents (see e.g. p. 1158, left-hand column, par. 3-6; p. 1245, Table 161-3; p. 1248, column 2, last par. - p. 1249, left-hand column, par. 3; p. 1250, left-hand column, par. 4 - right-hand column, par. 2; p. 1251, left-hand column, par. 4 - right-hand column, par. 2; p. 1252, left-hand column, par. 2-3).

The treatment of these diseases by the presently claimed compounds has been found not inventive (see items **V.iv(g)4-6**).

In the absence of an unexpected effect, such as synergy, due to the coadministration of the Salinosporamide A derivatives with anti-microbial agents, the presence of an inventive step cannot at present be recognised, since the skilled person would have expected at least some beneficial effect from the combination of these compounds, in the absence of indications to interactions or other non-beneficial effects obtained by the combination in question.

8. In conclusion, in the absence of comparative data and/or convincing arguments showing a surprising effect when using Salinosporamide A and its derivatives for the treatment of microbial illnesses over the prior art compounds lactacystin β-lactone and PS-519, an inventive step cannot be recognised at present.